

REMARKS

Applicants have amended the claims in response to the outstanding Office Action dated June 28, 2004. Applicants respectfully request that the present response and terminal disclaimer be entered.

THE AMENDMENTS

Applicants have canceled claims 1-21, 23-35, and 38 without prejudice.

Applicants have canceled claim 17 to delete reference to certain diseases that the Examiner contends are not enabled. Applicants have added claim 79 to recite, in part, the originally claimed diseases. Support for this amendment is found throughout the specification as originally filed (see, e.g., page 37, line 4 to page 38, line 13).

Applicants have amended claim 22 in response to the Examiners' rejections and to further clarify the subject matter. Applicants have inserted the phrase -- ring, wherein each of these groups is optionally substituted, and wherein said heterocyclic ring is a three to nine membered saturated or unsaturated mono-, bi-, or tri-heterocyclic ring system wherein each ring contains up to three heteroatoms selected from O, N, or S -- after the term "heterocyclalkyl" in the definition of R in claim 22. Support for this amendment is found throughout the specification as originally filed (see, e.g., page 11, lines 1-11 and 20-32, page 10, lines 25-32).

Applicants have amended claim 22 to clarify the specific leaving group intended in "Y" by inserting the phrase:

-- selected from F, Cl, Br, I, arylsulfonyloxy, alkylsulfonyloxy, trifluoromethanesulfonyloxy, OR', SR', -OC=O(R'), or -OPO(R⁶)(R⁷);

wherein R' is an aliphatic group, an aryl group, an aralkyl group, a carbocyclic group, an alkyl carbocyclic group, a heterocyclic group, or an alkyl heterocyclic group;

wherein R⁶ and R⁷ are independently selected from R or OR; --

after "group". Support for this amendment is found throughout the specification as originally filed (see, e.g., page 12, lines 7-17).

Applicants have amended claim 22 to clarify that the word "isosteres" in the definition of R² therein refer to isosteres of carboxylic acids. Specifically applicants have deleted the phrase "or esters or amides or isosteres thereof" after the term "CH₂CO₂H" and inserted the following phrase:

- i) CO₂H, or an ester, or an amide thereof; or R² is an isostere of said CO₂H; or
- ii) CH₂CO₂H, or an ester, or an amide thereof; or R² is an isostere of said CH₂CO₂H; --.

Support for this amendment is found throughout the specification as originally filed (see, e.g., page 13, lines 13-20).

Applicants have amended the definition of radical R³ by deleting the phrase:

-- a group capable of fitting into the S2 sub-site of a caspase; and --

and inserting the phrase -- selected from H, a side chain of a natural α-amino acid, or a substituted or unsubstituted group having a molecular weight up to about

140 Daltons selected from aliphatic, aryl, aralkyl, heterocyclyl or heterocyclylalkyl ring wherein said heterocyclyl or heterocyclylalkyl ring is a three to nine membered saturated or unsaturated mono-, bi-, or tri-heterocyclic ring system wherein each ring contains up to three heteroatoms selected from O, N, or S. --

Applicants had previously recited the radical "R" within the definitions of radical "R¹" and radicals "R⁴" and "R⁵" in claim 22. Applicants have amended claim 22 to delete the radical "R" and recite "R⁹" within the definition R⁴ and R⁵. R⁹ is now properly distinguished from "R" in the definition of R¹. Applicants have also clarified the specific substituents intended for the definition of "R" and "R⁹" by inserting the phrase:

-- wherein the optional substituents on said C₁₋₁₂ aliphatic group or aryl, aralkyl, heterocyclyl, or heterocyclylalkyl ring is independently selected from, from halogen, -R¹¹, -OR¹¹, -OH, -SH, -SR¹¹, acyloxy, substituted or unsubstituted Ph or OPh, -NO₂, -CN, -NH₂, -NHR¹¹, -N(R¹¹)₂, -NHCOR¹¹, -NHCONHR¹¹, -NHCON(R¹¹)₂, -NR¹¹COR¹¹, -NHCO₂R¹¹, -CO₂R¹¹, -CO₂H, -COR¹¹, -CONHR¹¹, -CON(R¹¹)₂, -S(O)₂R¹¹, -SONH₂, -S(O)R¹¹, -SO₂NHR¹¹, -NHS(O)₂R¹¹, =O, =S, =NNHR¹¹, =NNR¹¹₂, =N-OR¹¹, =NNHCOR¹¹, =NNHCO₂R¹¹, =NNHSO₂R¹¹, or =NR¹¹; and

wherein each R¹¹ is independently selected from a C₁₋₁₂ aliphatic group or a substituted C₁₋₁₂ aliphatic group. --

after the phrase "substituted aliphatic group" in the definition of R⁴ and R⁵ in claim 22. Support for this amendment is found throughout the specification as originally filed (see, e.g., page 11, lines 20-32).

Applicants have recited a list of substituents

for the ring system in the definition of R⁴ and R⁵ in claim 22 to further clarify the substituents intended.

Therein applicants have added the phrase:

-- wherein said ring system is optionally substituted with one or more groups independently selected from halogen, -R⁹, -OR⁹, -OH, -SH, -SR⁹, protected OH (such as acyloxy), phenyl (Ph), substituted Ph, -OPh, substituted -OPh, -NO₂, -CN, -NH₂, -NHR⁹, -N(R⁹)₂, -NHCOR⁹, -NHCONHR⁹, -NHCON(R⁹)₂, -NR⁹COR⁹, -NHCO₂R⁹, -CO₂R⁹, -CO₂H, -COR⁹, -CONHR⁹, -CON(R⁹)₂, -S(O)₂R⁹, -SONH₂, -S(O)R⁹, -SO₂NHR⁹, or -NHS(O)₂R⁹;

wherein each R⁹ is independently selected from an aliphatic group or a substituted aliphatic group; -- after the term "or sulfur;". Support for this amendment is found throughout the specification as originally filed (see, e.g., page 15, lines 30-32 and page 16, lines 1-6).

Applicants have canceled claims 23-35 and added claims 39-81 to more clearly recite the subject matter of the original claims. Support for this amendment is found throughout the specification as originally filed (see, e.g., page 9, line 10 to page 18, line 25).

Applicants have amended claim 36 to recite the compound structures and numbers from Table 1 in the specification. Support for this amendment is found in the specification at pages 19-48.

Applicants have canceled claim 38 and added claim 78 to more clearly recite the subject matter of the original claim. Support for this amendment may be found throughout the specification as originally filed (see, e.g., page 31, line 22 to page 37, line 3).

None of the above amendments adds any new matter. These amendments are further discussed below in the context of the Examiners' rejections.

THE REJECTIONS

35 U.S.C. § 112, Second Paragraph

Claims 1-38 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter of the invention. As noted above, applicants have canceled claims 1-21, 23-35, and 38. Applicants address below the Examiner's specific rejections.

i) The Examiner contends that in "claim 1 one cannot say for sure which disease is alleviated by treatment with a caspase inhibitor and which disease is not". Applicants have canceled claim 1 thus obviating this rejection.

ii) The Examiner contends that the term "heterocyclyl" in the definition of R and R³ is indefinite because it is not known which heteroatoms are present and how many of each is present. Applicants have amended the definition of radical R and R³ in claim 22 to clarify which heteroatoms are intended and also point out to the Examiner that claim 22 already specified that "each ring contains up to three heteroatoms" thus obviating this rejection. Added claims 42, 46, 49, 51, 53, 55, 57, 59-61, 63-64, and 66-69 also include this clarification.

iii) The Examiner contends that in "the definition of Y it is unclear which leaving group is intended and which one is not or under which conditions the leaving group is supposed to leave." As discussed *supra*, applicants have amended claim 22 to recite the leaving groups intended thus obviating this rejection.

iv) The Examiner contends that it is "unclear which ester or amide of COOH is intended" in the definition of R² and also that it is unclear "which isosteres are intended." Applicants point to page 12, lines 18-32 and page 13, lines 1-20 in the specification to provide support for the ester and amides intended. Additionally, applicants have amended claim 22 to clarify that the word "isosteres" therein refers to isosteres of the carboxylic acid groups. Accordingly, applicants request that the Examiner withdraw this rejection. Added claims 41, 45, 48, 51-52, 54, 57-58, 60-62, 64-65, and 67-69 also incorporate this clarification.

v) The Examiner contends that it is "unclear which group is capable of fitting into the S2 sub-site of a caspase and which one is not" in the definition of R³. As discussed *supra*, applicants have clarified the definition of radical R³ in amended claim 22. Specifically, applicants have amended the definition of R³ to recite:

-- R³ is selected from H, a side chain of a natural α-amino acid, or a substituted or unsubstituted group having a molecular weight up to about 140 Daltons selected from aliphatic,

aryl, aralkyl, heterocyclyl or heterocyclylalkyl ring wherein said heterocyclyl or heterocyclylalkyl ring is a three to nine membered saturated or unsaturated mono-, bi-, or tri-heterocyclic ring system wherein each ring contains up to three heteroatoms; --

Accordingly, applicants respectfully request that the Examiner withdraw this rejection. Added claims 42, 46, 49, 51, 53, 55, 57, 59-61, 63-64, and 66-69 also incorporate this clarification.

For the reasons set forth above, applicants respectfully request that the Examiner withdraw his 35 U.S.C. § 112, second paragraph rejections.

35 U.S.C. § 112, First Paragraph

Claims 1-8, 17-29 and 38 stand rejected for lack of enablement under 35 U.S.C. § 112, first paragraph.

Applicants have canceled claims 1-8, 17-21, 23-29 and 38. Applicants address the Examiners specific rejections below for added method of treatment claim 79.

Claim 79 contains an amended list of diseases and is enabled by the evidence of record provided herein.

Applicants respectfully disagree that applicants' compounds could not be used to treat the recited diseases. As set forth in applicants' specification, caspase inhibition had been linked to the treatment of the claimed diseases at the time of applicants' filing date (see, e.g., specification at page 4, line 19 to page 5, line 4). These links continue to be confirmed.

For example, early work established that IL-1 β , a cytokine released from stimulated monocytic cells, is an early and primary player in activating inflammation pathways associated with immune disorders and disease (see, e.g., specification page 2, lines 9-18; Geiger et al.¹). Therefore, it has been established that caspase-1 (also known as ICE) inhibitors are therapeutically useful because they block the formation of active IL-1 β .

Importantly, this utility has been demonstrated *in vivo*.

Ku reports that administration of an ICE (caspase-1) inhibitor is effective at reducing IL-1 β levels *in vivo*, and in reducing and alleviating inflammatory-associated symptoms and disease states.² In particular, Ku shows that an ICE inhibitor that reduces IL-1 β levels *in vivo* can have profound effects on inflammation as demonstrated in a mouse with collagen- or LPS-induced arthritis, an accepted animal model for rheumatoid arthritis in humans. In fact, the data clearly show that treatment with the ICE inhibitor is more effective on the induced inflammation than treatment with steroidal anti-inflammatory agents used to treat human inflammation. Importantly, the level of ICE inhibition demonstrated by applicants' compounds (see, e.g., specification pages 49-54) would also be expected to be therapeutically useful.

¹ Geiger, T. et al., "Neutralization of Interleukin-1 β Activity *in vivo* with a Monoclonal Antibody Alleviates Collagen-induced Arthritis in DBA/1 Mice and Prevents the Associated Acute-phase Response," Clin. Exper. Rheumatol., 11, pp. 515-22 (1993) (Exhibit A9).

² Ku, G. et al., "IL-1 β Converting Enzyme Inhibition Blocks Progression of Type II Collagen-Induced Arthritis in Mice," Cytokine, 8, pp. 377-386 (1996) (Exhibit A6).

Similarly, B. E. Miller reports that parenteral administration of an ICE inhibitor selectively inhibits mature IL-1 β production *in vivo*.³

These studies demonstrate a correlation between *in vitro* and *in vivo* data relating to inhibition of IL-1 β . Thus, applicants' *in vitro* data are sufficient to support the claimed methods directed to treating various diseases by inhibiting interleukin-1 β *in vivo*.

As recited throughout applicants' specification as filed, the diseases recited in applicants' claims are associated with caspases. These diseases are IL-1- (inflammatory or immunoregulatory) or apoptosis-mediated (see, page 3, lines 6-28). The links between IL-1, apoptosis and caspases have been established (see, page 1, line 31 to page 4, line 4). Furthermore, as discussed below, the art in the field confirms the link between caspases and applicants' recited diseases. Applicants will demonstrate that a link exists between, each of the claimed diseases. Therefore, applicants are entitled to claims directed to the treatment of the various diseases recited in claim 91.

A correlation between sepsis and septic shock and IL-1 has been established by Ohlsson.⁴ Ohlsson showed that eight of ten rabbits treated with *Escherichia coli* endotoxin died within 48 hours (Ohlsson, p. 550). In contrast, nine of ten rabbits treated with *Escherichia*

³ Miller, B. E. et al., "Inhibition of Mature IL-1 β Production in Murine Macrophages and a Murine Model of Inflammation by WIN 67694, an Inhibitor of IL-1 β Converting Enzyme," J. Immunol., 154, pp. 1331-38 (1995) (Exhibit A7).

coli endotoxin and IL-1ra "survived seven days and appeared to make a full recovery" (Ohlsson, p. 550). This study demonstrates that reduction of IL-1 levels is a viable treatment for sepsis and septic shock.

Humans with sepsis have responded favorably to IL-1ra treatment in a clinical trial reported by Boermeester.⁵ Boermeester treated 26 patients who were suffering from sepsis syndrome with intravenous IL-1ra (Boermeester, p. 739). The patients were evaluated after 72 hours (Boermeester, p. 740). The patients that had been treated with IL-1ra had reduced levels of several inflammatory mediators (Boermeester, p. 742).

Boermeester also discusses a study that demonstrated improved survival in a primate septic shock model (Boermeester, p. 739). Thus, a correlation between reduction in IL-1 levels and the treatment of sepsis and septic shock has been demonstrated.

Additionally, applicants have advanced VX-799, a small molecule caspase inhibitor, into preclinical development for sepsis in 2001.⁶

As discussed above, Ku has also reported a correlation between IL-1 inhibition and treating inflammation and rheumatoid arthritis based on a mouse model of rheumatoid arthritis.

⁴ Ohlsson, K. et al., "Interleukin-1 Receptor Antagonist Reduces Mortality from Endotoxic Shock," Nature, 348, pp. 550-552 (1990) (Exhibit A20).

⁵ Boermeester, M.A. et al., "Interleukin-1 Blockade Attenuates Mediator Release and Dysregulation of the Hemostatic Mechanism During Human Sepsis," Arch. Surg., 130, pp. 739-748 (1995) (Exhibit A24).

⁶ Vertex Pharmaceuticals Form 10-K for 2002, p. 11. (Exhibit 1)

Furthermore, applicants have advanced VX-740, a small molecule ICE/caspase-1 inhibitor into phase II proof of concept clinical studies for both rheumatoid arthritis and osteoarthritis. Recently completed Phase IIa studies with VX-740 in human patients showed a dose-dependent trend towards improvement in signs and symptoms of disease as measured by ACR20 response rates after 12 weeks.⁷

ICE (caspase-1) inhibitors have been shown to be effective at reducing the severity and mortality of induced pancreatitis in rats.⁸ Norman demonstrated, in a rat model of pancreatitis, that animals treated with the ICE inhibitor VE-13045, a novel, irreversible peptidyl ICE inhibitor, have a mortality rate of 22% as compared to a mortality rate of 68% for untreated animals (Norman, p. 116). Moreover, animals receiving the ICE inhibitor exhibited significantly less severe pancreatitis (Norman, p. 116). Norman concludes that "[t]he current series of experiments demonstrates the efficacy of VE-13045 in antagonizing ICE *in vivo* and confirms the importance of ICE in the processing and secretion of IL-1" (Norman, p. 117). Norman's study further demonstrates the profound detrimental effect of IL-1 β during acute pancreatitis and therapeutic applications of ICE blocked in this disease.

⁷ Vertex Pharmaceuticals Form 10-K for 2002, p. 12. (Exhibit 1)

⁸ Norman, J. et al., "Severity and Mortality of Experimental Pancreatitis are Dependent on Interleukin-1 Converting Enzyme (ICE)," J. Interferon Cytokine Res., 17, pp. 113-118 (1997) (Exhibit A28).

McCarthy has demonstrated that IL-1 plays a role in graft-versus-host disease (GVHD).⁹ McCarthy teaches that the *in vivo* administration of human IL-1ra "reduce[d] the immunosuppression and mortality of GVHD" in mice that had received a graft of hematopoietic stem cells (McCarthy, p. 1915). McCarthy thereby establishes a link between IL-1 and GVHD and between IL-1 and autoimmune disease.

Lan has treated another autoimmune disease, glomerulonephritis, with IL-1ra.¹⁰ Lan evaluated the effect of IL-1ra treatment on the progression of established rat accelerated anti-GBM disease, a severe model of glomerulonephritis (Lan, p. 1307). Lan determined that IL-1ra treatment over days 7 to 21 halted the progression of established disease (Lan, p. 1308). Lan concluded that IL-1 plays a key role in the progressive/chronic phase of renal injury in experimental crescentic glomerulonephritis, an autoimmune disease (Lan, p. 1303). Lan thereby establishes a link between IL-1 and autoimmune disease, and confirms the usefulness of ICE (caspase-1) inhibitors in the treatment of autoimmune diseases.

As discussed above, ICE (caspase-1) has been linked to the regulation of apoptosis in neurodegenerative diseases (see, specification page 4,

⁹ McCarthy, P.L., "Inhibition of Interleukin-1 by an Interleukin-1 Receptor Antagonist Prevents Graft-Versus Host Disease," Blood, 78, pp. 1915-1918 (1991) (Exhibit A49).

¹⁰ Lan, H.Y., "Interleukin-1 Receptor Antagonist Halts the Progression of Established Crescentic Glomerulonephritis in the Rat," Kidney Internat., 47, pp. 1303-1309 (1995) (Exhibit A32).

line 25 to page 5, line 4). ICE is, therefore, a useful target for diseases associated with apoptotic pathways.

Specifically, *in vivo* inhibitory effects of ICE have been demonstrated via an apoptotic pathway. Endres has shown an ICE inhibitor (z-VAD.FMK) to exhibit neuroprotective effects in a mouse model of mild ischemia.¹¹ Endres demonstrated that mice treated with 120 ng of z-VAD.FMK 6 hours after reperfusion decreased infarct size and neurologic deficits at 72 hours, and sustained these protective effects for at least 7 days (Endres, p. 242). Thus, Endres supports a correlation between ICE inhibitors and the treatment of stroke and other CNS injuries (Endres, p. 246).

Rouquet has also shown an ICE inhibitor to be effective in reducing *in vivo* liver apoptosis in mice.¹² This type of apoptosis is found in viral and inflammatory liver diseases (Rouquet, p. 1192). Rouquet concludes that "in vivo inhibition of ICE-dependent apoptosis ... represents an attractive approach for treating liver injuries, including ... those caused by inflammatory, viral and autoimmune diseases" (Rouquet, p. 1194).

Yaoita also supports the attenuation of apoptotic effects by administration of an ICE inhibitor.¹³ Yaoita assessed the administration of the ICE-like

¹¹ Endres, M. et al., "Attenuation of Delayed Neuronal Death After Mild Focal Ischemia in Mice by Inhibition of the Caspase Family," J. Cereb. Blood Flow and Metab., 18, pp. 238-247 (1998) (Exhibit A15).

¹² Rouquet, N. et al., "ICE Inhibitor YVADcmk is a Potent Therapeutic Agent Against *In Vivo* Liver Apoptosis," Curr. Biol., 6, pp. 1192-1195 (1996) (Exhibit A33).

¹³ Yaoita, H. et al., "Attenuation of Ischemia/Reperfusion Injury in Rats by a Caspase Inhibitor," Circulation, 97, pp. 276-281 (1998) (Exhibit A25).

inhibitor ZVAD-fmk in a rat model for myocardial reperfusion injury, and showed that ZVAD-fmk was effective in reducing myocardial reperfusion injury, which could be at least partially attributed to the attenuation of cardiomyocyte apoptosis (Yaoita, p. 279).

In addition to its role in the regulation of IL-1, apoptosis, and diseases related thereto, ICE (caspase-1) has been linked to the conversion of pro-IGIF to the pro-inflammatory cytokine IGIF, also known as IL-18, and to IFN- γ production *in vivo* (see, specification page 3, lines 9-13). IFN- γ has been shown to contribute to the pathology associated with a variety of inflammatory, infectious and autoimmune disorders and diseases. ICE is, therefore, also a useful target for IL-18-based therapeutic strategies because of its role in producing active IL-18.

ICE (caspase-1) activity has also been linked to intestinal inflammation, including colitis, inflammatory bowel disease, and Crohn's disease. Specifically, Siegmund discusses the role of ICE in the processing of IL-18.¹⁴ Siegmund showed that blockade of the inflammatory cytokine IL-18 in a mouse model of DSS-induced colitis significantly decreased histological signs of inflammation (Siegmund, p. 5).

A study on human myocardial tissue indicated that IL-1 β and IL-18 are present in the heart after ischemia.¹⁵ Pomerantz has shown that administration of an

¹⁴ Siegmund, B., "Interleukin-1 β Converting Enzyme (Caspase-1) in Intestinal Inflammation," Biochem. Pharmacol., 64, pp. 1-8 (2002) (Exhibit A37).

¹⁵ Pomerantz, B.J. et al., "Inhibition of Caspase 1 Reduces Human Myocardial Ischemic Dysfunction via

ICE inhibitor before the onset of ischemia resulted in the attenuation of ischemia-induced myocardial dysfunction (Pomerantz, p. 2874). Pomerantz therefore supports a correlation between ICE and IL-18 inhibition and the treatment of degenerative diseases such as myocardial ischemia.

Li has linked caspase inhibition and spinal cord injury treatment.¹⁶ Administration of a broad caspase inhibitor to mice having spinal cord injuries "reduced post-traumatic lesion size and improved neurological recovery" (Li, p. 339). The observations included that IL-1 β levels after spinal cord injury, were 17-fold higher in injured mice than in control mice. However, treatment of the injured mice with a caspase inhibitor, led to a 52.3% reduction in IL-1 β levels (Li, p. 335, and Table 2, p. 337). According to Li, this study showed that "following acute surgical decompression and stabilization, local delivery of caspase inhibitors can be one of the components of an SCI treatment protocol in humans" (Li, p. 341).

Li's expectation that these results are applicable to humans is well grounded because both apoptosis and activation of caspase-3 have been found in humans having spinal cord injuries.¹⁷ According to Emery, "apoptotic cell death is observed from 3 hours to 8 weeks

Inhibition of IL-18 and IL-1 β ," Proc. Natl. Acad. Sci., 98, pp. 2871-2876 (2001) (Exhibit A27).

¹⁶ Li, M. et al., "Functional Role and Therapeutic Implications of Neuronal Caspase-1 and -3 in a Mouse Model of Traumatic Spinal Cord Injury," Neurosci., 99, pp. 333-342 (2000) (Exhibit 2).

¹⁷ Emery, E. et al., "Apoptosis After Traumatic Human Spinal Cord Injury," J. Neurosurg., 89, pp. 911-920 (2000) (Exhibit 3).

after traumatic human [spinal cord injuries]" (Emery, p. 918).

Activation of caspase-3 has been shown in humans suffering from traumatic brain injury.¹⁸ Furthermore, caspase inhibition has been shown to be effective at treating traumatic brain injury in an animal model.¹⁹ In particular, administration of a broad caspase inhibitor "improved motor and cognitive neurological dysfunction after [traumatic brain injury]" in rats (Knoblauch, p. 1168). The injured animals performed better than control animals in several tests (Knoblauch, p. 1161). These studies confirm the relationship between caspases and traumatic brain injury and demonstrate the efficacy of treating traumatic brain injury with caspase inhibitors.

Caspase inhibition has been linked to treatment of amyotrophic lateral sclerosis (ALS).²⁰ A broad caspase inhibitor demonstrated "inhibition of disease progression and extended survival in a transgenic mouse model of ALS (Li II, p. 338). Elevated caspase levels, particularly ICE levels, have been found in human ALS patients.²¹

¹⁸ Härter, L. et al., "Caspase-3 Activity is Present in Cerebrospinal Fluid from Patients with Traumatic Brain Injury," J. Neuroimmunol., 121, pp. 76-78 (2001) (Exhibit 4, first page only).

¹⁹ Knoblauch, S.M. et al., "Multiple Caspases are Activated after Traumatic Brain Injury: Evidence for Involvement in Functional Outcome," J. Neurotrauma, 19, pp. 1155-1170 (2002) (Exhibit 5).

²⁰ Li, M. et al., "Functional Role of Caspase-1 and Caspase-3 in an ALS Transgenic Mouse Model," Science, 288, pp. 335-339 (2000) (Exhibit 6; "Li II").

²¹ Ilzecka, J. et al., "Interleukin-1 β Converting Enzyme/Caspase-1 (ICE/Caspase-1) and Soluble APO-1/Fas/CD 95 Receptor in Amyotrophic Lateral Sclerosis Patients,"

Ethical considerations may have limited this study. Nevertheless, it indicates that the same disease state exists in human ALS patients as exists in animal models of ALS. It would, therefore, be believable to a skilled practitioner that caspase inhibition would be useful in methods for treating ALS.

Caspase inhibition has been linked to the treatment of multiple sclerosis.²² In a mice model (experimental autoimmune encephalomyelitis), a caspase-1 (ICE) inhibitor reduced encephalomyelitis at some phases of the disease course.²³ Caspase-1 levels have been shown to be elevated in the brains of humans that had multiple sclerosis.²⁴ Furthermore, in a human cell line that is relevant to multiple sclerosis, a caspase inhibitor "was able to block the cytotoxic effects of TNF- α /IL-1 β in a dose-dependent manner" (Ming, p. 17).

Caspases have been linked to atherosclerosis. Increased apoptosis is thought to be correlated with plaque complications in atherosclerosis, such as rupture.²⁵ Jacob demonstrated that caspase-3 is elevated

Acta Neurolog. Scand., 103, pp. 255-258 (2001) (Exhibit 7, first page only).

²² Ahmed, Z. et al., "A Role for Caspase-1 and -3 in the Pathology of Experimental Allergic Encephalomyelitis," Am. J. Path., 161, pp. 1577-1586 (2002) (Exhibit 8).

²³ Furlan, R. et al., "Caspase-1 Regulates the Inflammatory Process Leading to Autoimmune Demyelination," J. Immunol., 163, pp. 2403-2409 (1999) (Exhibit 9, first page only).

²⁴ Ming, X. et al., "Caspase-1 Expression in Multiple Sclerosis Plaques and Cultured Glial Cells," J. Neurol. Sci., 197, pp. 9-18 (2002) (Exhibit 10, first page only).

²⁵ Jacob, T. et al., "Differential Proteolytic Activity and Induction of Apoptosis in Fibrous Versus Atheromatous Plaques in Carotid Atherosclerotic Disease," J. Vasc.

in human plaques, which corroborates earlier work on "carotid artery plaques" (Jacob, p. 618).

Cell death has been linked to various types of graft rejection, including in coronary artery bypass grafts.²⁶ In human tissue, caspase-3 was "expressed in all areas of the grafts" (Wang, p. 323).

Caspases have been linked to heart disease. A caspase-3 inhibitor has been shown to reduce myocardial stunning in a "working-heart rat model" (Ruetten, p. 2069).²⁷ Caspase-3 has also been linked to heart disease in humans.²⁸

Caspases have also been linked to heart failure. Specifically, caspases have been shown to be elevated in patients undergoing heart failure.²⁹ Furthermore, the protein caspase inhibitor p35 had "a positive impact on contractility" in a rabbit model of heart failure (Laugwitz, p. 2061).³⁰

Surg., 33, pp. 614-620 (2001) (Exhibit 11, first page only).

²⁶ Wang, A.Y. et al., "Expression of Apoptosis-related Proteins and Structural Features of Cell Death in Explanted Aortocoronary Saphenous Vein Bypass Grafts," Cardiovasc. Surg., 9, pp. 319-328 (2001) (Exhibit 12, first page only).

²⁷ Ruetten, H. et al., "Inhibition of Caspase-3 Improves Contractile Recovery of Stunned Myocardium, Independent of Apoptosis-inhibitory Effects," J. Am. Coll. Cardiology, 38, pp. 2063-2070 (2001) (Exhibit 13).

²⁸ Mallat, Z. et al., "Evidence of Apoptosis in Arrhythmogenic Right Ventricular Dysplasia," N. Eng. J. Med., 335, pp. 1190-1196 (1996) (Exhibit 14).

²⁹ Birks, E. et al., "Quantitative Myocardial Cytokine Expression and Activation of the Apoptotic Pathway in Patients Who Require Left Ventricular Assist Devices," Circul., 104 (suppl. I), pp. I233-I240 (2001) (Exhibit 15, first page only).

³⁰ Laugwitz, Karl-Ludwig et al., "Blocking Caspase-Activated Apoptosis Improves Contractility in Failing

Similarly, caspases have been linked to myocardial infarction. Administration of a caspase inhibitor reduced ischemia in a rat model.³¹ Elevated levels of caspase-3 and apoptosis have been observed in human heart tissue after acute myocardial infarction.³² According to Baldi, these results in combination with "experimental models" shows that "anti-apoptotic therapy (i.e. treatment with ... a broad caspase inhibitor) reduced infarct size ... thus opening new avenues in the diagnosis and treatment of ischemic heart disease (Baldi, p. 173).

Idun Pharmaceuticals, in a February 5, 2002 press release announced plans to move their small molecule caspase inhibitor IND-6734 into Phase I studies in human patients for myocardial infarct.³³ The decision was based on positive results in rodents where "IDN-6734 decreased heart muscle damage by 27% to 55% when administered after a simulated heart attack and in pigs where IDN-6734 "provided a 22% to 32% reduction in heart muscle damage". The result in pigs was noted as a significant step in the decision to enter human clinical trials because of the similarity in response to injury and therapeutic treatment between pig and human hearts.

Arndt confirmed a correlation between ICE, IL-18, and IL-1 β and acute lung injury using a murine model

Myocardium," Human Gene Therapy, 12, pp. 2051-2063 (2001) (Exhibit 16).

³¹ Yaoita, H. et al., "Attenuation of Ischemia/Reperfusion Injury in Rats by a Caspase Inhibitor," Circulation, 97, pp. 276-281 (1998) (Exhibit A25).

³² Baldi, A. et al., "Apoptosis and Post-infarction Left Ventricular Remodeling," J. Mol. Cell. Cardiol., 34, pp. 165-174 (2002) (Exhibit 17, first page only).

³³ PRNewswire Press Release for Idun Pharmaceuticals, 2/05/2002. (Exhibit 18)

of hemorrhage or endotoxemia.³⁴ The studies implicate ICE and IL-18 in the modulation of the development of acute lung injury after endotoxemia (Arndt, p. 708).

Apoptosis, inflammatory cytokines, such as IL-1, and/or caspases have been linked to other diseases as follows. Hoek demonstrates a link between caspases and excess dietary alcohol intake disease.³⁵ Ravage has linked inflammatory cytokines and burns.³⁶ Ehrmann³⁷ and Bantel³⁸ have linked caspases and hepatitis. Mongan has linked caspases and haemorrhagic shock.³⁹ Hauser has

³⁴ Arndt P.G., et al., "Expression of Interleukin-18 in the Lung After Endotoxemia or Hemorrhage-induced Acute Lung Injury," A.J. Respir. Cell Mol. Biol., 22, pp. 708-713 (2000) (Exhibit A46).

³⁵ Hoek, J.B. & Pastorino, J.G., "Excess Dietary Alcohol Intake Disease," Alcohol, 27, pp. 63-68-590 (2002) (Exhibit 19, abstract only).

³⁶ Ravage, Z.B., "Mediators of Microvascular Injury in Dermal Burn Wounds," Inflammation, 22, pp. 619-29 (1998) (Exhibit 20, abstract only).

³⁷ Ehrmann, J. Jr. et al., "Apoptosis-related Proteins, BCL-2, BAX, FAS, FAS-L and PCNA in Liver Biopsies of Patients with Chronic Hepatitis B Virus Infection," Pathol. Oncol. Res., 6, pp. 130-135 (2000) (Exhibit 21, abstract only).

³⁸ Bantel, H. et al., "Caspase Activation Correlates With the Degree of Inflammatory Liver Injury in Chronic Hepatitis C Virus Infection," Hepatology, 34, pp. 758-67 (2001) (Exhibit 22).

³⁹ Mongan, P.D., "Pyruvate Improves Redox Status and Decreases Indicators of Hepatic Apoptosis During Hemorrhagic Shock in Swine," Am. J. Physiol. Heart Circ. Physiol. 283, pp. H1634-644 (2002) (Exhibit 23, abstract only).

linked caspases and renal disease.⁴⁰ Yang has linked caspases and kidney disease.⁴¹

Additionally, Idun Pharmaceuticals, in a January 31, 2002 press release, announced successful completion of a Phase I clinical study with their small molecule caspase inhibitor IDN-6556 in patients with mild hepatic impairment.⁴² Idun also announced plans to move IDN-6556 forward into Phase II clinical trials for individuals with hepatitis C virus infections, alcoholic liver disease and acute alcoholic hepatitis. These clinical trial announcements by both Idun Pharmaceuticals and applicants' further support the utility of caspase inhibitors for the treatment in humans of the diseases recited in claim 79.

As discussed above, applicants have demonstrated that caspase activation is useful in the treatment of the diseases recited in claim 79. Applicants' specification coupled with the knowledge in the art provides the skilled artisan with the requisite assurance, without requiring undue experimentation, that the claimed methods have the asserted utility.

For all of the reasons set forth above, applicants request that the Examiner withdraw this section 112, first paragraph rejection.

⁴⁰ Hauser, P. & Oberbauer, R., "Tubular Apoptosis in the Pathophysiology of Renal Disease," Wien Klin. Wochenschr. 114, pp. 671-677 (2002) (Exhibit 24, abstract only).

⁴¹ Yang, B. et al., "Caspase-3 and Apoptosis in Experimental Chronic Renal Scarring," Kidney Int., 60, pp. 1765-1776 (2001) (Exhibit 25, abstract only).

⁴² PRNewswire Press Release for Idun Pharmaceuticals issued on 1/31/02 (Exhibit 26).

Obviousness-Type Double Patenting

The Examiner has rejected claims 1-38, under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over claims 1-59 of U.S. Patent No. 6,689,784. To overcome this obviousness-type double patenting rejection, applicants hereby submit a terminal disclaimer under 37 CFR 1.321 (b) and (c), disclaiming the terminal portion of any patent granted on the above-identified patent application which would extend beyond the expiration date of U.S. Patent No. 6,689,784. Applicants note that a filing of a terminal disclaimer to obviate a rejection based on nonstatutory double patenting is not an admission of the propriety of the rejection. Quad Environmental Technologies Corp. v. Union Sanitary District, 946 F.2d 870 (Fed. Cir. 1991). The filing of a terminal disclaimer simply serves the administrative function of removing the rejection of double patenting, and raises neither a presumption nor estoppel on the merits of the rejection.

CONCLUSION

Applicants respectfully request that the Examiner consider the foregoing remarks and allow the pending claims to pass to issue. Applicants would like to thank the Examiner for careful consideration of this application. If it is believed that a telephone call would expedite prosecution, the Examiner is invited to contact the undersigned at (617) 444-6467. The Commissioner is also authorized to charge any fees (or credit any overpayments) to Deposit Account Number: 50-0725, reference number VPI/01-109 DIV US.

Respectfully submitted,



Michael C. Badia
Reg. No. 51,424
Agent for Applicants

Vertex Pharmaceuticals Inc.
130 Waverly Street
Cambridge, MA 02139-4242
Tel.: (617) 444-6467
Fax.: (617) 444-6483